Further Experiments with Tryptamine: A Low-Yielding but Simple Synthesis of DPT By Way of Reductive Amination, 1st Attempt

Preface

Curiosity got to me once again. So a hunt for propionaldehyde (propanal) began. Not the easiest reagent to locate, but a bottle was found eventually. The theory is that it is the same synthesis as DMT, but swap the (para)formaldehyde for the three carbon aldehyde, install that twice for two propyl groups. DET can be made analogously, with acetaldehyde instead. But there are already a few write-ups online for DET, and the substance did not seem interesting enough. Could be a good one though as well.

I gave it a shot with DPT, and it turns out that it could be made this way, a truly sacred substance, one of the greats, an immense power, and all quite easily at home. Something mind-blowing.

First some chemical backgrounds:

Chem Info

Tryptamine (T, 3-(2-Aminoethyl)indole) $C_{10}H_{12}N_2$
Mol. weight: **160.22 g/mol**; Melting Point: **118 °C**

Very soluble in acetone, alcohols; insoluble in chloroform, water (negligible).
Appearance: white to light sandy tan needles or powder.

DPT (N,N-Dipropyltryptamine, 3-[2-(Dipropylamino)ethyl]indole) $C_{16}H_{24}N_2$
Mol. weight (freebase): **244.375 g/mol**, Mol. weight (HCl): **280.84 g/mol**
Melting Point (HCl): **174 – 178 °C** (Shulgin), pKa (HCl): 8.6; The freebase is soluble in alcohols, chloroform, ether, dioxane, and is insoluble in water. The HCl is soluble in water.
Appearance: The freebase is a viscous, thick, colourless oil, but it might be able to crystallize (have yet to investigate). The HCl is a fine white powder.

Propionaldehyde (propanal) C_3H_6O, Mol. weight: **58.08 g/mol**, colourless liquid with a musty smell. A bit like very ripe fruit with a hint of sourdough bread. Its fumes are heavier than air, highly flammable. Boiling point: 46 – 50 °C, Density**: 0.81 g/cm^{-3}**

Sodium Borohydride ($NaBH_4$): Mol. weight: **37.83 g/mol**, white powder/ crystals, hydroscopic, forms a cake exposed to air.

Minutia chems
For the **TLC eluent: ethyl acetate** (EtOAc), **methanol** (MeOH) or EtOH, **hexane** (or heptane), **25% ammonia**
For extraction: **DCM** (dichloromethane) or chloroform, and anhydrous **$MgSO_4$** to dry the DCM layer a
Used in A/B extraction for purification of tryptamine (optional): **Acetic Acid** (GAA), as well as **sodium hydroxide** (NaOH)
To dissolve the tryptamine, MeOH is used as the solvent
In the final stage to help reveal the DPT HCl we use isopropyl alcohol (**IPA**), and methyl *tert*-butyl ether (**MTBE**).
Industrial grade $CaCl_2$ to make an ice bathe that can go to -20 °C (optional). Find a bucket used for de-icing sidewalks (helps if it is winter in a cold climate).

The Reaction

Purifcation of T (optional)
51 g of darker, tan coloured tryptamine was first A/B extracted. Tryptamine acetate in water was formed and cleaned with DCM in a separatory funnel. The DCM picks up gunk or this dark nasty stuff crashes out and sticks to the sep. funnel walls, sinks to the bottom. Discard the DCM to waste.

Then filter the aq. layer into a glass dish and heat gently to remove any remaining DCM. Finally add dilute NaOH to raise pH above 11 or so, tryptamine crashes out, filter, wash with water, and dry. Remember that there is a lot of water in between the tryptamine so suck at the pump in a Büchner funnel for a longer time. Fan dry for a few hours.

Standard stuff, now we begin with **47.78 g or 0.298 mol** of much better looking **tryptamine**. However, it is a question whether this step is necessary, maybe those impurities don't interfere with the reaction. But if you are obsessive, and have time on your hands, go ahead and purify your tryptamine before proceeding.

Actual Start
Plan to do 4 cycles or additions of propanal and $NaBH_4$. First add the propanal then that boro.

0) Prepare a $CaCl_2$ bathe. In a large glass dish mix 1.5 kg of $CaCl_2$ and 5 L water, add some crushed ice, and set in a freezer (or outside). It cools slowly to -20 C. Recommended to prepare a second dish like this now to change at the second cycle or so. Still this is insufficient cooling, and a complete hassle compared to using a dry ice and acetone bath, did not have sufficient cooling once again for this reaction. Highly recommended for a 50 g reaction to use dry ice. For smaller amounts, 5 or 15 g, $CaCl_2$ should be sufficient.
But for this amount, use only if your access to dry ice is restricted.

1) Calculate the amount of **propanal**
Cycles 1 and 3: A **2x mol equivalent to the tryptamine**, calculate as 0.6 mol or **43 mL** each cycle
Cycles 2 and 4: A **1.5x mol equivalent to the tryptamine**, calculate as 0.45 mol or **32 mL** each for these two cycles. A total of 2.1 mol of propionaldehyde or 122 g or **150 mL**. Measure out in a graduated cylinder, cover and set aside.

2) Calculate the amount of **$NaBH_4$**
Cycles 1 and 3: A **1.1x mol equivalent to the tryptamine**, calculate as 0.328 mol or **12.4 g** each cycle
Cycles 2 and 4: A **0.75x mol equivalent to the tryptamine**, calculate as 0.22 mol or **8.3 g** each for these two cycles. A total of 1.096 mol. Weigh out **41.5 g** and set aside. For each cycle use about half the molar amount as the propionaldehyde.

For reductive amination the aldehyde will most likely not react quickly and all in the first round, so an excess is required. Acidic conditions are not incorporated, they would speed up imine formation but are also conducive to a Pictet-Spengler reaction.
However, I was uncertain as to the exact numbers at the time, so the quantities are taken from Sawdust and Honey's 5-MeO-MiPT synthesis.

3) Dissolve the tryptamine in MeOH**,** I have found that a **9x amount of MeOH to tryptamine** is good. You could dissolve in much less, but with later $NaBH_4$ additions, the mass becomes quite thick. Dissolve the tryptamine in 430 mL methanol and pour into a 3-neck round bottom flask with a large egg magnet for stirring.

4) For TLC the eluent was roughly 10 mL EtOAc + 0.5 mL MeOH + 0.5 mL hexane + 0.25 – 0.4 mL 25% ammonia. You should mix up the mobile phase shortly before taking a reading, and make sure to prepare a fresh mixture every time. The time between cycles in the reaction could be a few hours, and in that time the ammonia will evaporate. Maybe hexane evaporates quicker than the rest as well. So make a fresh one each time with the roughly the same proportions. Once again I completely forgot about this, and the after the 2nd cycle the spots are too low (ammonia didn't pull up). Mix up a larger amount, and keep in a bottle with a GL45 top closed.

5) Prepare in a small glass vial or bottle **2 mL fresh MeOH and 4 drops of the tryptamine/ MeOH** mixture as the standard for TLC. Test and record a rather low *Rf* of 0.24. But this is ok, as all of the other compound are less polar, the nitrogen becomes more impeded with addition of propyl groups. Bonding with the stationary phase (the silica on the TLC plate) becomes more difficult, hence they travel up the plate further, carried better by the less polar mobile phase, or eluent. Use the same concentration when taking samples of the reaction mixture further along after cycles.

6) The internal temperature of the flask is 5 °C with the **first propanal addition**. While the temperature of the $CaCl_2$ ice-water bath is -17 °C. No change with the propanal addition. But there is a reaction going on. The electrons from the nitrogen are staging a nucleophilic attack on the propanal! Temperature continues dropping as the RBF cools.
After **40 min**, temp drops to -13 °C. Begin the **first $NaBH_4$ addition**.

7) Pouring just a small amount of **$NaBH_4$ the temperature rises quickly to 5 °C**. Continue shaking in small amounts, and still go too fast. The trick is right at the start to have a low and very few teaspoonfuls drive the temperature up, as the foaming begins you really need to step back. Wait. Try again with a small amount see if temperatures jump, if the temp is stabile between 0 and 5 °C then begin carefully to shake in more boro (was using a weighing boat). Could take longer to add all the boro working with large amounts (use dry ice!). But toward the end of the addition you can add faster. It seems that it stabilizes towards the end of the addition and temperatures no longer climb. **Just be very careful at the start. This goes for every cycle.**

8) Let it to spin for **2 hours**, was away and the temperature had jumped to 25 °C, something happened with the cooling or maybe the temperature crossed a certain threshold and the NaBH4 suddenly bubbled off, it was quenched. Not good, higher temps are conducive to a Pictet-Spengler reaction, and ring cyclization. Could inadvertently form a substituted beta-carboline. Maybe Tetrahydroharman. But not sure as to exact conditions.

9) Second addition of propanal. This time adding raises the temperature, possibly indicating unreacted boro. Believe that I took TLC before the addition, and it already showed little tryptamine left.

10) Second addition of boro, after this one TLC could have been low and unclear. Pour way too fast and temp hits 38 C. Could have seriously screwed up here.

TLC after two cycles shows no hint of tryptamine, however there are 3 or 4 spots. The uppermost is brighter after the 2nd cycle compared to the end of cycle 1. Key take-away that this was too long of a reaction time, no need to wait for 1h30 min - 2 hours after completing boro addition. Adding the boro itself takes 30 minutes, and after 1 cycle it seems as if most tryptamine had reacted.

So pour in propanal the first time, wait maybe 30 minutes, and then begin adding the boro, once done adding boro, let react for 45 min. Take TLC and take note! Left spot tryptamine control, middle Co spot (tryptamine on top of cycle 1), right just the reaction mixture after the end of the cycle 1.
Add propanal second time, let react 30 min, add boro, once done let react for 45 min. Take TLC with the fresh eluent and look to see if the tryptamine is gone. Do three lanes but maybe tryptamine, cycle 1, cycle 2. Decide whether to do a mini-cycle to get to all propyltryptamine, and possibly a bit of dipropyltryptamine, with no tryptamine.

And finally: let temps hover between **-5 – 5 °C**, but maybe a short temp spike to 15 °C is not the end of the world.

11) Switch to a new ice bathe, but it is only at -8 °C or so. Poor cooling. **Continue cycle 3 and 4**, but with shorter reaction times after completing the addition of boro. Take about 1 hour 20 min after boro addition, and after propanal addition, maybe 30 minutes for these two cycles.

It was late, and wanted to get the reaction over. This could have been **a mistake, adding the second propyl group should prove to be more difficult** prove to be more difficult. Steric hindrance from the bulky group, the nitrogen now sheathed in armor, feeling itchy and uncomfortable, and only sluggishly galloping away to the propanal's under protected carbonyl carbon. So it follows that one needs longer reaction times, and TLC does seem to indicate this. After the 4th cycle, take a note of TLC but it does look like that the lower of the three upper spots seems to have disappeared as compared with the 3rd cycle. Slower to fade. Probably indicates that there is no propyltryptamine left after all. However there is more than one spot indicating that the product is not pure, or maybe that somehow a **5th cycle was required.**

The Work-Up

1) After peeking at the TLC after the 4th cycle, decide to call it a day. Reaction over and too lazy to distill off the methanol, so just **pour in 400 mL of water. Roughly equivalent to the reaction mixture**. There is an **immediate white precipitation**, and yellow spots floating to the surface forming a layer. Still some bubbling to indicate unreacted boro releasing hydrogen. Go to sleep.

2) Next day, notice these is no bubbling, reaction has stopped. To wash beakers, pour in another 100 mL water. A **white mass** has formed on the **bottom** and a **yellow layer on top**. What has likely occurred with the pouring in of water is that borate salts from reacted $NaBH_4$ had crashed out or partially dissolved in the water. As well the yellow freebase and other organics insoluble in water had formed a layer on top. But it looks easy to pick up with DCM now. This could be a helpful development, it should make things easier at small or medium scales for those poor suckers unable to distill.

3) Carefully **extract with DCM in a sep. funnel**. **Use 175 mL** and do not shake, separates slowly, but no emulsion is formed. Consistency of the mixture is perfect. Nonetheless, chloroform would separate faster. Extract **two more times with 100 mL each time**. Could have worked more diligently and made one more extraction.

4) Filter into a glass dish to evaporate over a hotplate. Mistake here, should have distilled off. Takes a long time to evaporate in a fume hood. Full day. And some DCM still remains trapped in the thick mass.

5) Pain to deal with such a sticky viscous orange-red mass, scrape most off of a plate. But losses are inevitable. Weigh by taring a beaker. Weight is 83.65 g. Now we must **separate the impurities from the DPT.**

6) Attempt to **vacuum distill** using a new (used) pump, but improperly set-up with no gauge to read the pressure.
In TiHKAL it is written that "The oily residue was distilled at **145 – 155 °C at 0.08 mm/Hg** to give 1.14 g *N*,*N*-dipropyltryptamine base as a white oil." So we could by that temperature.
Applying a vacuum the reaction mixture begins to boil violently. This could be the residual DCM boiling off. Raising the temperature there is boiling and condensation on the beaker, and Claisen still head; but nothing coming over into the condenser. The glassware is too large for 100 mL or less of this sticky mass.
Temperature climbs over 150 °C and I notice smoke being produced, probably the product being burnt, but I don't care much and continue on. Out of the pump exhaust I no longer know or try to understand whether it is exhaust fumes or burnt tryptamine smoke. Both. Anguish and despair constant bedfellows in the latter stages of these sort of experiments.

Had set the heating mantle temperature to a max of 180 °C maybe. But finally a thick slightly off-white oil starts to trickle home. And the temperatures fall from a maximum of 170 °C and fluctuate somewhat between **135 and 150 °C**. Close to Shulgin's.

Continues to trickle a bit, slowly, and all at once with not much having come over as compared to the amount in the boiling flask, stops and temperatures fall to maybe 90 °C.

Call it quits and dismantle the pagan contraption. I very well could have skipped the vacuum distillation, and attempted a hot heptane extraction of the DCM. It did work for 5-MeO-MiPT albeit with an increased amount of heptane as compared to DMT. Might have avoided potential losses this way, by not dealing with a tricky distillation.

7) In the boiling flask have about 39 g of a polymerized? sticky red oil. In the receiving flask, have a slightly white just slightly yellow oil with a weight of 15.34 g. Off-white, but clear.

8) Dissolve the oil in a 6x IPA amount mostly **following Shulgin's work-up**. Use 100 mL IPA also washing glassware of residual oil. Now we will salt the freebase. Calculate mol equivalent based on DPT freebase or 0.066 mol. Take 36% HCl which is 11.64 mol/L so need about 5.7 mL. Dilute this in 5 mL distilled water.

9) Under magnetic stirring add in the HCl, at a certain point with a few drops, there is a sudden darkening of colour, and then I check the pH and as usual overshoot the pH, it drops to 2.19. Was expecting to use more HCl, this indicates that not all of the oil is DPT, impurities have vacuum distilled over as well.

10) Now the DPT HCl does not crash out of the IPA, so how to get it out? Distilling off or evaporating the IPA, would leave us with the impurities mixed in.
What Shulgin does is pour in ethyl ether to crash out the product, what we can do is use a safer alternative. Let's see if pouring in MTBE work
Pour in **50 mL MTBE** under stirring, and within a few seconds, very spectacularly, it reveals itself! The beaker is filled with ivory white DPT HCl. His Majesty has been revealed.

11) Filter and wash with a bit of IPA, the DPT looks to be very pure. Nicest white powder imaginable. Weight of the 1st crop: 8.333 g

12) Set the mother liquor in a freezer, and hope that more product falls out. It does. Weight of the 2nd crop: 2.666 g. **Total weight 11 g**, this is 0.0392 mol, began with 0.298 mol tryptamine. So this is a **13.1% yield**.

13) But is it really DPT? Besides taking a bioassay (eating some) we can also procede with a melting point test. I melt a sample in a capillary tube in a Thiele tube. Watching closely see that the **sample melts** somewhere between **172 – 176 °C.** Very close to numbers in TiHKAL. Seems good.

Attempts to recover more product were fruitless. To the mother liquor pour in 50 mL more MTBE and 50 mL IPA, freeze as well, but there is no precipitation. Evaporate off, and there do seem to be some spots of DPT HCl, but too difficult to separate from the impurities. Not worth it.

Later to the reaction mass that did not distill over, I add to dissolve 450 mL IPA and then add about 22 mL diluted (by half) HCl. Let pH drop to 5.8, but there is no change. Adding MTBE, there is no precipitation, and later evaporating off everything, just back to the same sticky red mass.

Conclusion

If you skip the distillation in this synthesis, and it should be possible, then it becomes even simpler. As well this is a route to DPT that doesn't require any exotic, and expensive reagents. The propionaldehyde is a bit more costly when compared to something like paraformaldehyde, but still well within reason when taking into account the product formed and its value.

Still those 11 g of product from 47 g of substrate are a puny yield from an incompetent chemist's first attempt at this compound. If with future revisions the yield improves to 50% lets say, then from 50 g tryptamine, one would end up close to 44 g of product, now would truly be something and DPT would have a place as well in the limelight.

Append(age)-ix

At the end if one is itching for more, naturally the question, "What other products can be made by a double reductive amination?" arises. Some have been made, while others are yours up for grabs to try and make. However, steric hindrance does seem like a hindrance with the bulkier ones. I assume reductive amination should work to make any mono-substituted tryptamine. But most of these are inactive.

Such as: NMT (N-Methyltryptamine NET), N-Ethyltryptamine (NiPT), N-Isopropyltryptamine (NsBT), N-sec-Butyltryptamine (supposedly active) and has made this way, NtBT (N-tert-Butyltryptamine) (supposedly active as well), NAT (N-Amyltryptamine), NHT (N-Hexyltryptamine), NBnT (N-Benzyltryptamine).

Here are two tables for the synthesis of some of the di-substituted tryptamines with the starting substrate of tryptamine, first table when adding aldehydes as reactants, second table a ketone and an aldehyde.

Note that all of these could be made starting with 5-MeO-Tryptamine to make the 5-MeO- counterpart (e.g. 5-MeO-DMT).

First a table when using only aldehydes:

Reactant for the 1st Two Cycles	**Reactant for the 2nd Two Cycles**	**Product Formed**
(para)formaldehyde	(para)formaldehyde	**DMT** (dimethyltryptamine)
acetaldehyde	formaldehyde	MET (methylethyltryptamine)
propionaldehyde	formaldehyde	MPT (methylpropyltryptamine)
butyraldehyde	formaldehyde	MBT (methylbutyltryptamine)
acetaldehyde	acetaldehyde	**DET** (diethyltryptamine)
propionaldehyde	acetaldehyde	EPT (ethylpropyltryptamine)
propionaldehyde	propionaldehyde	**DPT** (dipropyltryptamine)
butyraldehyde	propionaldehyde	PBT (propylbutyltryptamine)
acrolein	formaldehyde	MALT(dethylallyltryptamine)
acrolein	acrolein	DALT(diallyltryptamine)

*Product in **bold** has been made via reductive amination

And using a ketone and an aldehyde:

Reactant for the 1st Two Cycles	**Reactant for the 2nd Two Cycles**	**Product Formed**
acetone	(para)formaldehyde	**MiPT**(methylisopropyltryptamine)
acetone	acetaldehyde	EiPT (ethylisopropyltryptamine)
acetone	propionaldehyde	PiPT (propylisopropyltryptamine)
butanone	formaldehyde	**MSBT** N-sec-butyl-N methyltryptamine)

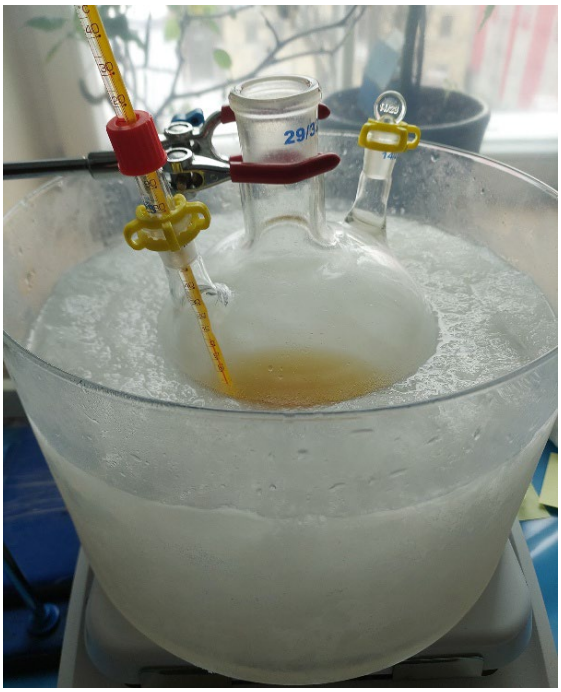
*Product in **bold** has been made via reductive amination (5-MeO-MiPT)

A post by xdragon on The Vespiary:
"Regarding asymmetric tryptamines, only the N-sec-alkyl-N-primary-alkyl-tryptamines (MIPT, EIPT, MSBT) can be made selectively by reductive alkylation of tryptamine with a ketone until complete conversion (NIPT, NSBT), then reductive alkylation with an appropriate aldehyde. This is because ketones will stop at the secondary amine, while aldehydes will alkylate all the way to the tertiary tryptamine."

So DiPT apparently can not be made with a double reductive amination.

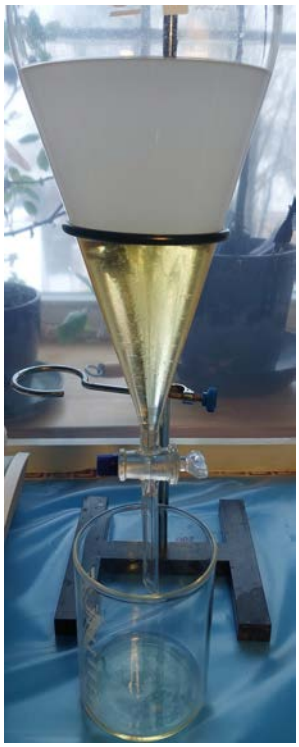
Some interweb links:
www.masterorganicchemistry.com/2017/09/01/reductive-amination/ **General info, chemistry**
www.thevespiary.org/talk/index.php?topic=16470.0 **Our local thread**
www.hyperlab.info/inv/index.php?s=&act=ST&f=17&t=30859&st=0 **Good info in Russian**
www.isomerdesign.com/pihkal/read/tk/9 **TiHKAL entry**

Images



Set-up in a $CaCl_2$ ice bath with magnetic stirring

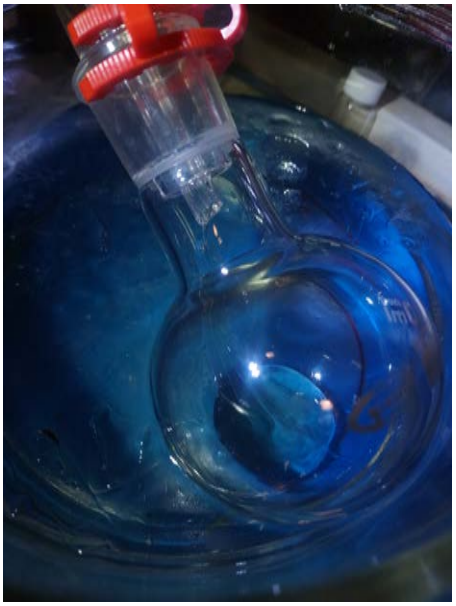
Pour in water after reaction, turns cloudy, and layers separate



Extract with DCM

Dry DCM layer with MgSO4

Vigourous bubbling as residual
DCM boils off during start of distillation



Oily substance starts flowing slowly into
the receiving flask

DPT HCl precipitates out
after
adding MTBE

Final Product, 1st
Crop

Melting point test
with a Thiele tube

TLC after 2 cycles, tryptamine on the left, On the right is the reaction showing no tryptamine and possibly NPT on the bottom

To contrast after cycle 1 there is still a faint spot of tryptamine but in cycle 2, the lower spot, NPT? is fainter and no T

Comparing cycle 2 (spot on the left, and cycle 3 (on the right), the lower spot continues to fade. Spots are not aligned (difference in concentration and misplacement?)

After cycle 3, cycle 4 in the middle, and Rx. Right lane is actually the distilled product, but too concentrated. Now it is clear that both cycle 4 and the distillate show very faint spots of what is likely NPT

Comparison of cycle 2 (accidentally applied too much sample), cycle 3, and cycle 4. In this image the very faint spot was not visible, and that is partially too early

Finally here is a outline of the synthesis, with some of the mechanisms and reactions. Not very detailed and not complete, just an attempt to draw one. Made just for your edutainment.